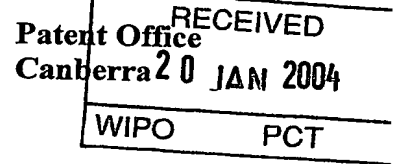


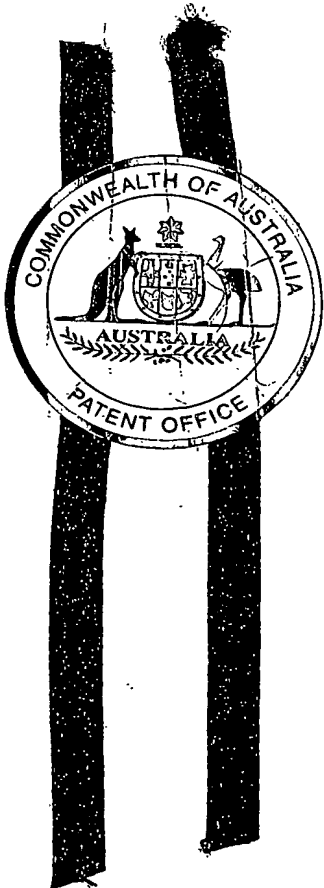


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I, JONNE YABSLEY, TEAM LEADER EXAMINATION SUPPORT AND
SALES hereby certify that annexed is a true copy of the Provisional specification
in connection with Application No. 2002953255 for a patent by CYTOPIA PTY
LTD as filed on 11 December 2002.



WITNESS my hand this
Eighth day of January 2004

JR Yabsley

JONNE YABSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

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AUSTRALIA
Patents Act 1990

Cytopia Pty Ltd

PROVISIONAL SPECIFICATION

Invention Title:

Protein Kinase Inhibitors

The invention is described in the following statement:

*Protein Kinase Inhibitors***FIELD OF THE INVENTION**

The present invention involves compounds represented by Formula (I) herein below, pharmaceutical compositions comprising such compounds and methods of suppressing the growth of cancers and other proliferative diseases.

BACKGROUND OF THE INVENTION

Normal cellular proliferation is a well-controlled balance between the rate of cell cycle progression and programmed cell death (apoptosis). This balance is maintained by the appropriate transmission of extracellular signals by intracellular signal transduction circuitry. In tumours this equilibrium becomes disturbed by either unrestrained completion of the cell cycle, or loss of normal apoptotic cell death. In many cases this deregulation comes about by the autonomous activation of the intracellular signal transduction circuitry that controls the cell cycle and apoptosis pathways. Central to the regulation of these pathways are members of the protein kinase family, and a promising avenue to the generation of treatments for hyperproliferative diseases such as cancer, are compounds that target those kinases involved in this regulation. Protein kinases are a family of enzymes that catalyse the phosphorylation of specific residues in proteins. In general protein kinases fall into several groups; those which preferentially phosphorylate serine and/or threonine residues, those which preferentially phosphorylate tyrosine residues and those which phosphorylate both tyrosine and Ser/Thr residues. Protein kinases are therefore key elements in signal transduction pathways responsible for transducing extracellular signals, including the action of cytokines on their receptors, to the nuclei, triggering various biological events. The many roles of protein kinases in normal cell physiology include cell cycle control and cell growth, differentiation, apoptosis, cell mobility and mitogenesis. Inappropriately high protein kinase activity has been implicated in many diseases resulting from abnormal cellular function. This might arise either directly or indirectly, for example by failure of the proper control mechanisms for a kinase, related for example to mutation, over-expression or inappropriate activation of the enzyme; or by over- or under-production of cytokines or growth factors also participating in the transduction of signals upstream or downstream of the kinase. In all of these instances, selective inhibition of the action of the kinase might be expected to have a beneficial effect. Diseases where aberrant kinase activity has been implicated include: diabetes; restenosis; atherosclerosis; fibrosis of the liver and kidney; ocular diseases; myelo- and lymphoproliferative disorders; cancer such as prostate cancer, colon cancer, breast cancer, head

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and neck cancer, leukemia and lymphoma; and, auto-immune diseases such as Atopic Dermatitis, Asthma, rheumatoid arthritis, Crohn's disease, psoriasis, Crouzon syndrome, achondroplasia, and thanatophoric dysplasia.

Protein kinases include, for example, but are not limited to, members of the Protein Tyrosine Kinase family (PTKs), which in turn can be divided into the cytoplasmic PTKs (CTKs) and the receptor PTKs (RTKs). The cytoplasmic PTKs include the SRC family, (including: BLK; FGR; FYN; HCK; LCK; LYN; SRC; YES and YRK); the BRK Family (including: BRK; FRK, SAD; and SRM); the CSK family (including: CSK and CTK); the BTK family, (including BTK; ITK; TEC; MKK2 and TXK), the Janus kinase family, (including: JAK1, JAK2, JAK3 and Tyk2), the FAK family (including, FAK and PYK2); the Fes family (including FES and FER), the ZAP70 family (including ZAP70 and SYK); the ACK family (including ACK1 and ACK2); and the Abl family (including ABL and ARG). The RTK family includes the EGF-Receptor family (including, EGFR, HER2, HER3 and HER4); the Insulin Receptor family (including INS-R and IGF1-R); the PDGF-Receptor family (including PDGFR α , PDGFR β , CSF1R, KIT, FLK2); the VEGF-Receptor family (including: FLT1, FLK1 and FLT4); the FGF-Receptor family (including FGFR1, FGFR2, FGFR3 and FGFR4); the CCK4 family (including CCK4); the MET family (including MET and RON); the TRK family (including TRKA, TRKB, and TRKC); the AXL family (including AXL, MER, and SKY); the TIE/TEK family (including TIE and TIE2/TEK); the EPH family (including EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHB1, EPHB2, EPHB3, EPHB4, EPHB5, EPHB6); the RYK family (including RYK); the MCK family (including MCK and TYRO10); the ROS family (including ROS); the RET family (including RET); the LTK family (including LTK and ALK); the ROR family (including ROR1 and ROR2); The Musk family (including Musk); the LMR family including LMR1, LMR2 and LMR3); and the SuRTK106 family (including SuRTK106).

Similarly, the serine / threonine specific kinases (STKs) comprise a number of distinct sub-families, including; the extracellular signal regulated kinases, (p42/ERK2 and p44/ERK1); c-Jun NH2-terminal kinase (JNK); cAMP-responsive element-binding protein kinases (CREBK); cAMP-dependent kinase (CAPK); mitogen-activated protein kinase-activated protein kinase (MAPK and its relatives); stress-activated protein kinase p38/SAPK2; mitogen-and stress-activated kinase (MSK); protein kinases, PKA, PKB and PKC inter alia. Additionally, the genomes of a number of pathogenic organisms possess genes encoding protein kinases. For example, the malarial parasite *Plasmodium falciparum* and viruses such as HPV and Hepatitis viruses appear to bear kinase related genes.

This invention is therefore directed to compounds that potentially modulate Protein Kinase signal transduction by affecting the enzymatic activity of RTKs, CTKs and/or STKs, thereby interfering

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with the signals transduced by such proteins. More particularly, the present invention is directed to compounds which modulate RTK, CTK and/or STK mediated signal transduction pathways as a therapeutic approach to cure many kinds of tumor.

In one embodiment, the method of the invention is used in the treatment of sarcomas, carcinomas and/or leukemias. Exemplary disorders for which the subject method can be used alone or as part of a treatment regimen include: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

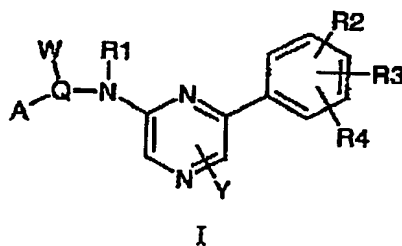
In certain embodiments, the method of the invention is used to treat disorders such as carcinomas forming from tissue of the breast, prostate, kidney, bladder or colon.

In other embodiments, the method of the invention is used to treat hyperplastic or neoplastic disorders arising in adipose tissue, such as adipose cell tumors, e.g., lipomas, fibrolipomas, lipoblastomas, lipomatosis, hibernomas, hemangiomas and/or liposarcomas.

SUMMARY OF THE INVENTION

The present inventors have found that a group of compounds based upon a disubstituted pyrazine scaffold are inhibitors of the growth and proliferation of cancer cells.

Accordingly, in a first aspect the present invention consists in a compound of the general formula



or pharmaceutically acceptable salts, hydrates, solvates, crystal forms or diastereomers thereof, wherein:

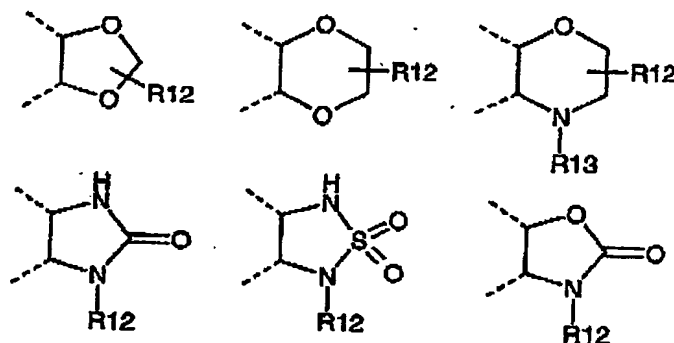
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R1 is H, C₁₋₆alkyl, C₁₋₆alkylNR5R6, C₁₋₆alkylNR5COR6, C₁₋₆alkylNR5SO₂R6, C₁₋₆alkylCO₂R5, C₁₋₆alkylCONR5R6, where R5 and R6 are each independently H, C₁₋₄alkyl, aryl, hetaryl,

C₁₋₄alkylaryl, C₁₋₄alkylhetaryl or may be joined to form an optionally substituted 3-8 membered ring optionally containing an atom selected from O, S, NR7 and R7 is selected from H, C₁₋₄alkyl.

R2, R3 and R4 are each independently H, halogen, C₁₋₄alkyl, OH, OC₁₋₄alkyl, CF₃, OCF₃, CN, C₁₋₄alkylNR8R9, OC₁₋₄alkylNR8R9, OCONR8R9, NR8R9, NR8COR9, NR8CONR9R10, NR8SO₂R9, COOR8, CONR8R9; and R8, R9, R10 are each independently H, C₁₋₄alkyl, C₁₋₄alkyl cycloalkyl, or may be joined to form an optionally substituted 3-8 membered ring optionally containing an atom selected from O, S, NR11; and R11 is selected from H, C₁₋₄alkyl, CF₃.

Alternatively, two of R2, R3 and R4, when located on adjacent carbon atoms, may be joined to form a ring system selected from:



where R12 is selected from H, C₁₋₄alkyl, CF₃ and R13 is selected from H, C₁₋₄alkyl, CF₃, COR10, SO₂R14; and R14 is selected from H, C₁₋₄alkyl.

Q is a bond, or C₁₋₄alkyl

W is selected from H, C₁₋₄alkyl, C₂₋₆alkenyl; where C₁₋₄alkyl or C₂₋₆alkenyl may be optionally substituted with C₁₋₄alkyl, OH, OC₁₋₄alkyl, NR15R16; and R15, and R16 are each independently H, C₁₋₄alkyl, C₁₋₄alkyl cycloalkyl, C₁₋₄alkyl cyclohetalkyl, aryl, hetaryl, or may be joined to form an optionally substituted 3-8 membered ring optionally containing an atom selected from O, S, NR17 and R17 is selected from H, C₁₋₄alkyl.

A is aryl, hetaryl optionally substituted with 0-3 substituents independently chosen from halogen, C₁₋₄alkyl, CF₃, aryl, hetaryl, OCF₃, OC₁₋₄alkyl, OC₂₋₆alkylNR18R19, Oaryl,

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Ohetaryl, CO₂R18, CONR18R19, NR18R19, C₁₋₄ alkylNR18R19, NR20C₁₋₄alkylNR18R19, NR18COR19, NR20CONR18R19, NR18SO₂R19; and R18, R19 are each independently H, C₁₋₄ alkyl, C₁₋₄ alkyl cyclohetaryl, aryl, hetaryl, C₁₋₄alkyl aryl, C₁₋₄ alkyl hetaryl, or may be joined to form an optionally substituted 3-8 membered ring optionally containing an atom selected from O, S, NR21; and R20 is selected from H, C₁₋₄ alkyl; and R21 is selected from H, C₁₋₄ alkyl.

Y is selected from H, C₁₋₄alkyl, OH, NR22R23, and R22, and R23 are each independently H, C₁₋₄alkyl.

In the above description it will be appreciated that:

C₁₋₄ alkyl means a straight or branched alkyl chain

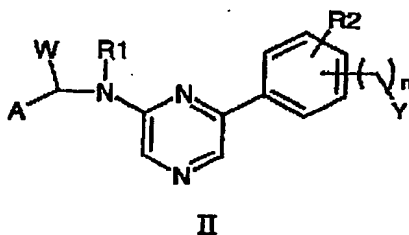
Aryl means unsubstituted or optionally substituted phenyl or naphthyl.

Hetaryl means an unsubstituted or optionally substituted 5- or 6-membered heteroaromatic ring containing one or more heteroatoms selected from O, N, S.

Cycloalkyl means a 3-8 membered saturated ring

Cyclohetaryl means a 3-8 membered saturated ring containing 1-3 heteroatoms selected from O, S, NR18, where R18 is H, C₁₋₄ alkyl, aryl, hetaryl.

In a further preferred embodiment the compound is selected from compounds of the general formula II.



or pharmaceutically acceptable salts, hydrates, solvates, crystal forms or diastereomers thereof, wherein:

R1 is H, C₁₋₄alkyl, C₁₋₆ alkylNR3R4, where R3 and R4 are each independently H, C₁₋₄alkyl, or may be joined to form an optionally substituted 3-8 membered ring optionally containing an atom selected from O, S, NR5 and R5 is selected from H, C₁₋₄ alkyl.

A is aryl, hetaryl optionally substituted with 0-3 substituents independently chosen from halogen, C₁₋₄ alkyl, CF₃, aryl, hetaryl, OCF₃, OC₁₋₄alkyl, OC₂₋₆alkylNR6R7, Oaryl, Ohetaryl, CO₂R6, CONR6R7, NR6R7, C₁₋₄ alkylNR6R7, NR8C₁₋₄alkylNR6R7, NR6COR7,

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NR8CONR6R7, NR6SO₂R7; and R6, R7 are each independently H, C₁₋₄ alkyl, C₁₋₄ alkyl cyclohetalkyl, aryl, hetaryl, C₁₋₄alkyl aryl, C₁₋₄ alkyl hetaryl, or may be joined to form an optionally substituted 3-8 membered ring optionally containing an atom selected from O, S, NR9; and R8 is selected from H, C₁₋₄ alkyl; and R9 is selected from H, C₁₋₄ alkyl.

R2 is 0-2 substituents independently selected from halogen, C₁₋₄alkyl, OH, OC₁₋₄alkyl, CF₃, OCF₃, CN, C₁₋₄alkylNR10R11, OC₁₋₄alkylNR10R11, CO₂R10, CONR10R11, NR10R11, NR10COR11, NR12CONR10R11, NR10SO₂R11; and R10, R11 are each independently H, C₁₋₄ alkyl; and R12 is selected from H, C₁₋₄ alkyl.

Y is H, OH, NR12R13; and R12, and R13 are each independently H, C₁₋₄ alkyl, or may be joined to form an optionally substituted 3-6 membered ring optionally containing an atom selected from O, S, NR14 and R14 is selected from H, C₁₋₄ alkyl.

n = 0-4

W is selected from H, C₁₋₄alkyl, C₂₋₆alkenyl; where C₁₋₄alkyl or C₂₋₆alkenyl may be optionally substituted with C₁₋₄alkyl, OH, OC₁₋₄alkyl, NR15R16; and R15, and R16 are each independently H, C₁₋₄ alkyl, C₁₋₄ alkyl cyclohetalkyl, or may be joined to form an optionally substituted 3-8 membered ring optionally containing an atom selected from O, S, NR17 and R17 is selected from H, C₁₋₄ alkyl.

In the above description it will be appreciated that:

C₁₋₄ alkyl means a straight or branched alkyl chain

Aryl means unsubstituted or optionally substituted phenyl or naphthyl.

Hetaryl means an unsubstituted or optionally substituted 5- or 6-membered heteroaromatic ring containing one or more heteroatoms selected from O, N, S.

Cycloalkyl means a 3-8 membered saturated ring

Cyclohetalkyl means a 3-8 membered saturated ring containing 1-3 heteroatoms selected from O, S, NR18, where R18 is H, C₁₋₄ alkyl, aryl, hetaryl.

In a preferred embodiment R1 is H.

In a further preferred embodiment the compound is selected from the group consisting of Chemistries 244, 284, 311, 312, 326, 328, 366, 367, 373 and 404 of Table 1.

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The compounds of this invention include all conformational isomers (eg. cis and trans isomers). The compounds of the present invention have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them. The compounds of formula I may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of protein kinases comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (eg. two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy and carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemossine, 3-methylhistidine, norvlin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methioine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain. Prodrugs also include phosphate derivatives of compounds of formula I (such as acids, salts of acids, or esters) joined through a phosphorus-oxygen bond to a free hydroxyl of compounds of formula I.

In a still further preferred embodiment the compound possesses *S* chirality at the chiral carbon bearing W, where W is C₁₋₄ alkyl or C₁₋₄alkylamino. The compound can be used as a purified isomer or as a mixture of any ratio of isomers. It is however preferred that the mixture comprises at least 70%, 80%, 90%, 95%, or 99% of the preferred isomer.

In a still further preferred embodiment the compound is selected from the compounds set out in Table 1.

In a second aspect the present invention consists in a composition comprising a carrier and at least one compound of the first aspect of the invention.

In a third aspect the present invention consists in a method of treating a tyrosine kinase-associated disease state, the method comprising administering a therapeutically effective amount of at least one compound of the first aspect of the invention or a therapeutically effective amount of a composition of the second aspect of the invention.

In a preferred embodiment of the present invention the disease state is selected from the group consisting of Atopy, such as Allergic Asthma, Atopic Dermatitis (Eczema), and Allergic Rhinitis; Cell Mediated Hypersensitivity, such as Allergic Contact Dermatitis and Hypersensitivity Pneumonitis; Rheumatic Diseases, such as Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, Juvenile Arthritis, Sjögren's Syndrome, Scleroderma, Polymyositis, Ankylosing Spondylitis, Psoriatic Arthritis; Other autoimmune diseases such as Type I diabetes, autoimmune thyroid disorders, and Alzheimer's disease; Viral Diseases, such as Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV), Human Papilloma Virus (HPV); Cancer, such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma, and carcinomas forming from tissue of the breast, prostate, kidney, bladder or colon, and neoplastic disorders arising in adipose tissue, such as adipose cell tumors, e.g., lipomas, fibrolipomas, lipoblastomas, lipomatosis, hibemomas, hemangiomas and/or liposarcomas.

As used herein the term "tyrosine kinase-associated disease state" refers to those disorders which result from aberrant tyrosine kinase activity and/or which are alleviated by inhibition of one or more of these enzymes.

The present invention provides pharmaceutical compositions comprising at least one of the compounds of the formula I or II capable of treating a kinase associated disorder in an amount effective therefore, and a pharmaceutically acceptable vehicle or diluent. The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

The compounds of the formula I or II may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intracisternal

injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the method of the present invention. In a preferred embodiment, the disease or condition is one in which the actions of eosinophils and/or lymphocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

The subjects treated in the above methods, in whom which cell growth inhibition is desired, are mammals, including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species, and preferably a human being, male or female.

The term "therapeutically effective amount" means the amount of the subject composition that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical

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composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example

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ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures

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but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilisers, preservatives, excipients and the like. The preferred lipids are the phospholipids and phosphatidyl cholines, both natural and synthetic. Methods to form liposomes are known in the art.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

Examples of other therapeutic agents include the following:
cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD401g and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), cholesterol biosynthesis inhibitors such as HMG CoA reductase inhibitors (lovastatin and simvastatin), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, aspirin, acetaminophen and cyclooxygenase inhibitors such as rofecoxib, steroids such as prednisolone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, antineoplastic agents such as azathioprine, VP-16, etoposide, fludarabine, cisplatin, doxorubicin, adriamycin, amsacrine, camptothecin, cytarabine, gemcitabine, vinblastine, vincristine, fluorodeoxyuridine, melphalan and cyclophosphamide, TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof.

When other therapeutic agents are employed in combination with the compounds of the present invention they may be used for example in amounts as noted in the Physician Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are known inhibitors or substrates of drug efflux systems or drug detoxification and excretory systems. Such systems include P-glycoprotein, multidrug resistance-associated protein, lung resistance protein and glutathione S-transferase isoenzymes alpha, mu, pi, sigma, theta, zeta and kappa. Co-administration of drugs known to inhibit or reduce the activity of these systems may increase the efficacy of the compounds described in the present invention through increasing the amount of therapeutic agent in the cell. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages, thus reducing the potential for adverse side effects. Examples of inhibitors or substrates for these systems include; verapamil, probenecid, dipyridamole, ethacrynic acid, indomethacin, sulfasalazine, buthionine sulfoximine, cyclosporin A and tamoxifen.

In the treatment or prevention of conditions which require protein tyrosine kinase inhibition an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

All publications mentioned in this specification are herein incorporated by reference.

15.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia before the priority date of each claim of this application.

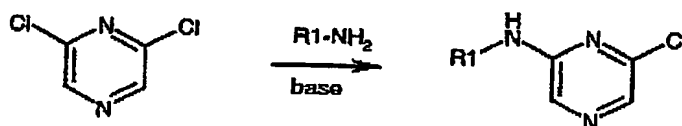
In order that the nature of the present invention may be more clearly understood preferred forms thereof will now be described by reference to the following non-limiting Examples.

MATERIALS AND METHODS:

Compound Synthesis

Compounds are generally prepared in a 2-step process starting from 2,6-dichloropyrazine.

The first step is a nucleophilic aromatic substitution to generate a monoamino-monohalo intermediate. (Scheme 1).



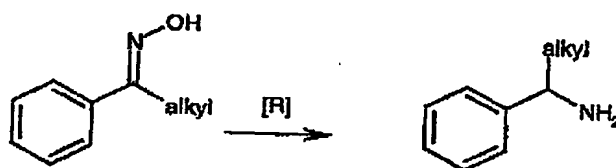
Scheme 1

The nucleophilic aromatic substitution is typically carried out by addition of a primary amine to the di-halogenated heterocycle in a solvent such as ethanol, isopropanol, tert-butanol, dioxane, THF, DMF, ethoxyethanol, toluene or xylene. The reaction is typically performed at elevated temperature in the presence of excess amine or a non-nucleophilic base such as triethylamine or diisopropylethylamine, or an inorganic base such as potassium carbonate or sodium carbonate.

Alternatively, the amino substituent may be introduced through a transition metal catalysed amination reaction. Typical catalysts for such transformations include Pd(OAc)₂/P(t-Bu)₃, Pd₂(dba)₃/BINAP and Pd(OAc)₂/BINAP. These reactions are typically out in solvents such as toluene or dioxane, in the presence of bases such as caesium carbonate or sodium or potassium tert-butoxide at temperatures ranging from room temperature to reflux.

The amines employed in the first step of the synthesis of these compounds are obtained commercially or are prepared using methods well known to those skilled in the art. Of particular interest are α -alkylbenzylamines which may be prepared through reduction of oximes (Scheme 2). Typical reductants include lithium aluminium hydride, hydrogen gas in the presence of palladium on charcoal catalyst, Zn in the presence of hydrochloric acid, sodium borohydride in the presence of a Lewis acid such as TiCl₄, ZrCl₄, NiCl₂ and MoO₃, or sodium borohydride in conjunction with Amberlyst H15 ion exchange resin and LiCl.

16.



Scheme 2

α -Alkylbenzylamines may also be prepared by reductive amination of the corresponding ketones. A classical method for such a transformation is the Leuckart-Wallach reaction, though catalytic conditions or alternative procedures (e.g. NH_4OAc , $\text{Na}(\text{CN})\text{BH}_3$) can also be used.

α -Alkylbenzylamines may also be prepared from the corresponding α -alkylbenzyl alcohols. Such methods include derivatisation of the hydroxyl as a mesylate or tosylate and displacement with a nitrogen nucleophile, such as phthalimide or azide which is converted to the primary amine using conventional synthetic methods; or, displacement of the hydroxyl with a suitable nitrogen nucleophile under Mitsunobu-like conditions. α -Alkylbenzyl alcohols can be prepared by reduction of the corresponding ketones with a reducing agent such as sodium borohydride in a solvent such as methanol. Alternatively, α -alkylbenzyl alcohols can be obtained through addition of an alkyl metal species (such as a Grignard reagent) to a benzaldehyde derivative, typically performed at room temperature or below in solvents such as tetrahydrofuran.

α -Alkyl benzylamines of high optical purity may be prepared from chiral α -alkyl benzyl alcohols using the methods outlined above. The chiral α -alkyl benzyl alcohols may be obtained through chiral reduction of the corresponding ketones. Chiral reducing methods are now well known in organic chemistry and include enzymatic processes, asymmetric hydrogenation procedures and chiral oxazaborolidines.

The second step of the synthesis typically involves a palladium mediated cross-coupling of the monoamino-monochloro intermediate with a suitably functionalised coupling partner. Typical coupling partners are boronic acids (Suzuki coupling: see for example Miyaura, N. and Suzuki, *Chem Rev.* 1995, 952457) or stannanes (Stille coupling: see for example Stille, J.K., *Angew. Chem., Int. Ed. Engl.*, 1986, 25, 508) (Scheme 3).



Scheme 3

The Suzuki coupling is the preferred coupling method and is typically performed in a solvent such as DME, THF, DMF, ethanol, propanol, toluene, or 1,4-dioxane in the presence of a base such as potassium carbonate, lithium hydroxide, caesium carbonate, sodium hydroxide, potassium fluoride or potassium phosphate. The reaction may be carried out at elevated

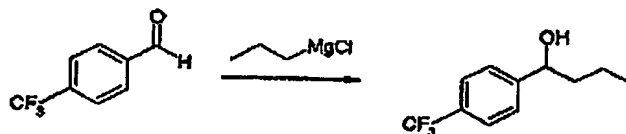
17.

temperatures and the palladium catalyst employed may be selected from $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{OAc})_2$, $[\text{PdCl}_2(\text{dppf})]$, $\text{Pd}_2(\text{dba})_3/\text{P}(\text{t-Bu})_3$.

The products formed from this reaction sequence may be further derivatised using techniques well-known to those skilled in the art. Alternatively, derivatisation of the mono-amino mono-chloropyrazine may be undertaken prior to displacement of the 6-chloro substituent. This derivatisation typically involves functionality originally present on the amine species and employs methods well known to those skilled in the art.

Representative syntheses are reported below.

18.

Example 1**1-[4-(Trifluoromethyl)phenyl]butan-1-ol**

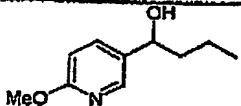
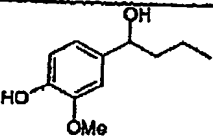
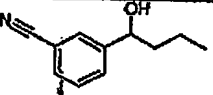
A 2M solution of propylmagnesium chloride in ether (4 ml, 8 mmol) was added to a solution of the aldehyde (1.14 g, 6.6 mmol) in dry THF (10 ml) cooled to 0 °C under N₂. The mixture was stirred for 16h at room temperature, after which time saturated ammonium chloride solution was added. The product was extracted into ethyl acetate, and the ethyl acetate layer dried and concentrated to furnish pure product (1.4g, 98%).

¹H-n.m.r. (CDCl₃) δ 0.94 (t, *J*=7.2Hz, 3H CH₃), 1.41 (m, 2H, CH₂), 1.75 (m, CH₂, 2H), 4.77 (br s, 1H, CH), 7.44-7.62(m, 4H, ArH)

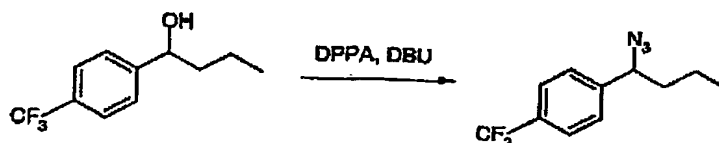
Using identical procedures the following compounds were prepared.

Compound	¹ H-n.m.r. (CDCl ₃)
	δ 0.95 (t, <i>J</i> =7.2Hz, 3H CH ₃), 1.39(m, 2H, CH ₂), 1.75(m, CH ₂ , 2H), 4.77(br s, 1H, CH), 7.41-7.63 (m, 4H, ArH)
	δ 0.94 (t, <i>J</i> =7.2Hz, 3H CH ₃), 1.40 (m, 2H, CH ₂), 1.76 (m, CH ₂ , 2H), 2.36 (s, 3H, CH ₃ -Ar), 4.65 (m, 1H, CH), 7.07-7.28 (m, 4H, ArH)
	δ 0.93 (t, 3H, <i>J</i> =7.2Hz, CH ₃), 1.37 (m, 2H, CH ₂), 1.75 (m, CH ₂ , 2H), 3.79 (s, 6H, 2xCH ₃ O), 4.61 (m, 1H, CH), 6.37 (m, 1H, Ar H), 6.50 (m, 2H, ArH)
	δ 0.96 (t, <i>J</i> =7.4Hz, 3H CH ₃), 1.47(m, 2H, CH ₂), 1.89 (m, CH ₂ , 2H), 2.36(d, <i>J</i> =4.8Hz, 1H, OH), 5.22 (m, 1H, CH), 6.93-7.03 (m, 1H, Ar-H), 7.16-7.26 (m, 2H, Ar-H)
	δ 0.93 (t, 3H, CH ₃), 1.16 (t, 6H, 2 x CH ₃), 1.2-1.8 (m, 4H, 2 x CH ₂), 3.34 (q, 4H, 2 x CH ₂), 4.56 (m, 1H, CH), 6.65 (m, 2H, Ar-H), 7.19 (m, 2H, Ar-H).

19.

	δ 0.93(t, 3H, CH ₃), 1.2-1.9 (m, 4H, 2 x CH ₂), 3.92 (s, 3H, CH ₃ O), 4.46 (t, 1H, CH), 6.73 (, 1H,), 7.59 (, 1H,), 8.07 (, 1H,).
	δ 0.93 (t, 3H CH ₃), 1.2-1.8 (m, 4H, 2 x CH ₂), 3.48 (d, 1H, OH), 3.90 (s, 3H, CH ₃), 4.60 (m, 1H, CH), 5.58 (m, 1H, ArOH), 6.80-6.89 (m, 3H, Ar-H).
	δ 0.93 (t, $J=7.0$ Hz, 3H, CH ₃), 1.24-1.48 (m, 2H, CH ₂), 1.60-1.80 (m, 2H, CH ₂), 1.92 (d, $J=3.4$ Hz, OH), 4.70-4.78 (m, 1H, CH), 7.41-7.67 (m, 4H, ArH)

20.

Example 2**1-(1-Azidobutyl)-4-(trifluoromethyl)benzene**

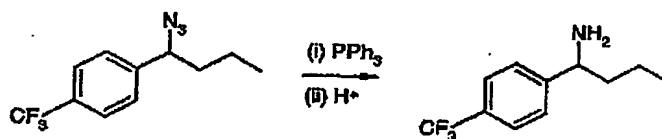
A solution of 1-[4-(trifluoromethyl)phenyl]butan-1-ol (1.4 g, 6.4 mmol) and diphenylphosphoryl azide (2.8 ml, 12.8 mmol) in THF (6 mL) cooled to -10°C under N₂ was treated with DBU (1.9 mL, 12.8 mmol). The resulting solution was stirred at room temperature for 20 hours and then diluted with a mixture of ether and H₂O. The organic phase was dried and concentrated and the residue purified by column chromatography using hexane:diethyl ethyl acetate (10:1) as eluent to furnish pure azide (0.85 g, 54%).

¹H-n.m.r. (CDCl₃) δ 0.94 (t, $J=7.2\text{Hz}$, 3H CH₃), 1.37 (m, 2H, CH₂), 1.75 (m, 2H, CH₂), 4.50 (t, 1H, CH), 7.42 (d, $J=7.8\text{Hz}$, 2H, ArH), 7.64 (d, $J=7.8\text{Hz}$, 2H, ArH)

Using identical procedures the following compounds were prepared.

Compound	¹ H-n.m.r. (CDCl ₃)
	δ 0.94 (t, $J=7.4\text{Hz}$, 3H CH ₃), 1.38 (m, 2H, CH ₂), 1.76 (m, 2H, CH ₂), 4.50 (t, $J=7.4\text{Hz}$, 1H, CH), 7.48-7.61 (m, 4H, ArH)
	δ 0.93 (t, $J=7.2\text{Hz}$, 3H, CH ₃), 1.36 (m, 2H, CH ₂), 1.76 (m, 2H, CH ₂), 2.37 (s, 3H, CH ₃), 4.37 (t, $J=7.4\text{Hz}$, 1H, CH), 7.07-7.26 (m, 4H, Ar-H)
	δ 0.93 (t, $J=7.4\text{Hz}$, 3H, CH ₃), 1.36 (m, 2H, CH ₂), 1.72 (m, 2H, CH ₂), 3.80 (s, 6H, 2 x CH ₃ - O), 4.34 (t, $J=7\text{Hz}$, 1H, CH), 6.41-6.45 (m, 3H, Ar-H)
	δ 0.96 (t, $J=7.4\text{Hz}$, 3H, CH ₃), 1.36 (m, 2H, CH ₂), 1.95 (m, 2H, CH ₂), 5.10 (t, 1H, OH), 6.98-7.08 (m, 1H, Ar-H), 7.18-7.25 (m, 2H, Ar-H)
	δ 0.94 (t, $J=7.2\text{Hz}$, 3H, CH ₃), 1.22-1.50 (m, 2H, CH ₂), 1.62-1.94 (m, 2H, CH ₂), 4.47 (t, $J=7.2\text{Hz}$, 1H, OH), 7.48-7.64 (m, 4H, Ar-H)

21.

Example 3**1-[4-(Trifluoromethyl)phenyl]butan-1-amine**

A mixture of 1-(1-azidobutyl)-4-(trifluoromethyl)benzene (0.84 g, 3.5 mmol) and triphenylphosphine (1.8 g, 6.9 mmol) in ethyl acetate (6 mL) and 10% HCl (6 mL) was stirred at room temperature for 64 h. The aqueous phase was collected and the organic phase extracted with 10% HCl (3 x 5 mL). The aqueous layers were combined and basified with 5M NaOH, and then extracted with ethyl acetate (5 x 15 mL). The organic phase was dried and concentrated to give pure amine (0.4 g, 54%).

^1H -n.m.r. (CDCl_3) δ 0.91 (t, $J=7.4\text{Hz}$, 3H CH_3), 1.31 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 3.97 (m, 1H, CH), 7.43 (dd, 2H, Ar-H), 7.58 (dd, 2H, Ar-H)

Using similar procedures the following compounds were prepared.

Compound	^1H -n.m.r. (CDCl_3)
	δ 0.91 (t, $J=7.4\text{Hz}$, 3H CH_3), 1.29 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 3.98 (m, 1H, CH), 7.42-7.59 (m, 4H, Ar-H)
	δ 0.91 (t, $J=6.8\text{Hz}$, 3H CH_3), 1.31 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.35 (s, 3H, CH_3 -Ar), 3.84 (m, 1H, CH), 7.03-7.21 (m, 4H, Ar-H)
	δ 0.90 (t, $J=7.4\text{Hz}$, 3H CH_3), 1.30 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 3.79 (s, 6H, CH_3 -O x 2), 3.8 (m, 1H, CH), 6.43 (m, 1H, Ar-H), 6.47-6.48 (m, 2H, Ar-H)
	δ 0.92 (t, $J=7.4\text{Hz}$, 3H CH_3), 1.26 (m, 2H, CH_2), 1.85 (m, 2H, CH_2), 4.44 (t, $J=7.4\text{Hz}$, 1H, CH), 6.90-7.17 (m, 3H, Ar-H)
	δ 0.91 (t, $J=7.0\text{Hz}$, 3H CH_3), 1.19-1.39 (m, 2H, CH_2), 1.47 (br s, 2H, NH_2), 1.57-1.68 (m, 2H, CH_2), 3.95 (t, $J=7.0\text{Hz}$, 1H, CH), 7.3-7.64 (m, 4H, Ar-H)

Example 4**3-Fluoro-N-methoxy-N-methylbenzamide**

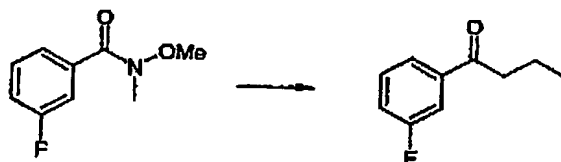
To a suspension of 3-fluorobenzoic acid (140 mg, 1 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (107 mg, 1.1 mmol) in dichloromethane (2.5 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (211 mg, 1.1 mmol) and the mixture stirred at room temperature for 75 h. The solvents were removed under reduced pressure and the residue chromatographed using ethyl acetate-hexane (4:6) to separate the pure product (130 mg, 71%).

¹H-n.m.r. (CDCl₃) δ 3.36 (s, 3H, N-Me), 3.55 (s, 3H, N-OMe), 7.1-7.2 (m, 1H, Ar), 7.3-7.5 (m, 3H, Ar)

Using similar procedures the following compounds were prepared.

Compound	¹ H-n.m.r. (CDCl ₃)
	δ 3.38 (s, 3H, N-Me), 3.55 (s, 3H, N-OMe), 7.3-7.4 (m, 1H, pyr), 7.95-8.05 (m, 1H, pyr), 8.65-8.70 (m, 1H, pyr), 8.94 (d, <i>J</i> =1.6Hz, 1H, pyr)
	δ 3.36 (s, 3H, N-Me), 3.55 (s, 3H, N-OMe), 7.03-7.12 (m, 2H, Ar), 7.70-7.7 (m, 2H, Ar)
	δ 3.35 (s, 3H, N-Me), 3.57 (s, 3H, N-OMe), 6.85 (d, <i>J</i> =8.8Hz, 2H, Ar), 7.63 (d, <i>J</i> =8.8Hz, 2H, Ar)
	δ 3.34 (s, 3H, N-Me), 3.57 (s, 3H, N-OMe), 6.93-6.97 (m, 1H, Ar), 7.12-7.26 (m, 3H, Ar)

23.

Example 5**1-(3-Fluorophenyl)butan-1-one**

To a solution of 3-fluoro-*N*-methoxy-*N*-methylbenzamide (130 mg, 0.71 mmol) in dry THF (2 mL) cooled to -10°C was added propyl magnesium chloride (532 μL , 2M solution in ether, 1.1 mmol) under nitrogen. The solution was stirred at -10°C for 1h and at room temperature for 75 min. The solution was poured into saturated aqueous ammonium chloride and the product extracted into ethyl acetate (3 x 25 mL). The organic layers were combined, washed with brine, dried (MgSO_4) and concentrated to give a pale yellow oil, which was purified by chromatography using ethyl acetate-hexane (1:9) to separate the pure product (78 mg, 66%).

^1H -n.m.r. (CDCl_3) δ 1.01 (t, $J=7.4\text{Hz}$, 3H, Me), 1.77 (sep, 2H, CH_2CH_3), 2.93 (t, $J=7.2\text{Hz}$, 2H, COCH_2), 7.15-7.30 (m, 1H, Ar), 7.35-7.50 (m, 1H, Ar), 7.60-7.70 (m, 1H, Ar), 7.70-7.80 (m, 1H, Ar).

Using similar procedures the following compounds were prepared.

Compound	^1H -n.m.r. (CDCl_3)
	δ 1.02 (t, $J=7.4\text{Hz}$, 3H, Me), 1.80 (sep, 2H, CH_2CH_3), 2.97 (t, $J=7.2\text{Hz}$, 2H, COCH_2), 7.36-7.46 (m, 1H, pyr), 8.20-8.30 (m, 1H, pyr), 8.7 (br d $J=4\text{Hz}$, 1H, pyr), 9.18 (br s, 1H, pyr).
	δ 1.00 (t, $J=7.4\text{Hz}$, 3H, Me), 1.76 (sep, 2H, CH_2CH_3), 2.91 (t, $J=7.2\text{Hz}$, 2H, COCH_2), 7.11 (t, $J=8.5\text{Hz}$, 2H, Ar), 7.94-8.02 (m, 2H, Ar)
	δ 1.01 (t, $J=7.4\text{Hz}$, 3H, Me), 1.68-1.86 (m, 2H, CH_2CH_3), 2.92 (t, $J=7.4\text{Hz}$, 2H, COCH_2), 7.36-7.55 (m, 2H, Ar), 7.82-7.93 (m, 3H, Ar)
	δ 1.00 (t, $J=7.4\text{Hz}$, 3H, Me), 1.67-1.85 (m, 2H, CH_2CH_3), 2.91 (t, $J=7.4\text{Hz}$, 2H, COCH_2), 7.59 (d, $J=8.8\text{Hz}$, 2H, Ar), 7.82 (d, $J=8.8\text{Hz}$, 2H, Ar)
	δ 1.00 (t, $J=7.4\text{Hz}$, 3H, Me), 1.68-1.86 (m, 2H, CH_2CH_3), 2.91 (t, $J=7.4\text{Hz}$, 2H, COCH_2), 6.55 (br s, 1H, OH), 6.92 (d, $J=9.2\text{Hz}$, 2H, Ar), 7.92 (d, $J=9.2\text{Hz}$, 2H, Ar)

24.

Example 6**1-(3-Chlorophenyl)butan-1-amine**

To a solution of 1-(3-fluorophenyl)butan-1-one (430 mg, 2.4 mmol) and ammonium acetate (1.09 g, 14.1 mmol) in methanol (10 mL) under nitrogen was added sodium cyanoborohydride (2.35 mL, 1M solution in THF, 2.35 mmol). The solution was stirred at room temperature for 38 h. after which time conc. HCl was added to give a pH~2. After bubbling had ceased the solvent was removed under reduced pressure and the residue dissolved in ethyl acetate and water. The organic phase was collected and the aqueous phase washed with ethyl acetate (20 mL). The aqueous phase was basified to pH ~10 with solid KOH and the product extracted into ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine, dried (Na₂SO₄) and concentrated to give a pure product (120 mg, 28%).

¹H-n.m.r. (CDCl₃) δ 0.90 (t, *J*=7.2Hz, 3H, CH₂CH₂CH₃), 1.17-1.44 (m, 2H, CH₂CH₂CH₃), 1.58-1.69 (m, 2H, CH₂CH₂CH₃), 1.81 (brs, 2H, NH₂), 3.88 (t, *J*=6.8Hz, CHNH₂), 7.20-7.32 (m, 4H, Ar)

Using similar procedures the following compounds were prepared.

Compound	¹ H-n.m.r. (CDCl ₃)
	δ 0.89 (t, <i>J</i> =7.2Hz, 3H, CH ₂ CH ₂ CH ₃), 1.16-1.38 (m, 2H, CH ₂ CH ₂ CH ₃), 1.57-1.69 (m, 2H, CH ₂ CH ₂ CH ₃), 7.74-2.14 (brs, 2H, NH ₂), 3.85 (brs, 1H, CHNH ₂), 6.78 (d, <i>J</i> =8.6Hz, 2H, Ar), 7.17 (d, <i>J</i> =8.6Hz, 2H, Ar)
	δ 0.88 (t, <i>J</i> =7.4Hz, 3H, CH ₂ CH ₂ CH ₃), 1.18-1.39 (m, 2H, CH ₂ CH ₂ CH ₃), 1.57-1.69 (m, 2H, CH ₂ CH ₂ CH ₃), 3.79 (t, <i>J</i> =6.8Hz, 1H, CHNH ₂), 6.74-6.84 (m, 1H, Ar), 7.10-7.19 (m, 1H, Ar)
	δ 0.88-0.94 (m, 6H, 2xMe), 1.47-1.56 (m, 5H, CH ₂ CH ₂ (CH ₃)NH ₂), 3.95 (t, <i>J</i> =6.6Hz, 1H, CH ₂ NH ₂), 7.20-7.37 (m, 5H, Ar)
	δ 1.07 (t, <i>J</i> =7.1Hz, 6H, 2 x CH ₂ CH ₃), 1.36 (d, <i>J</i> =6.2Hz, 3H, CHMe), 2.64 (q, 4H, 2 x CH ₂ CH ₃), 2.87 (t, <i>J</i> =6.3Hz, 2H, OCH ₂ CH ₂ N), 4.01-4.07 (m, 3H, OCH ₂ CH ₂ N + CHMe), 6.86 (d, <i>J</i> =8.7Hz, 2H, Ar), 7.25 (d, <i>J</i> =8.7Hz, 2H, Ar)

25.

	δ 0.91 (t, $J=7.4$ Hz, 3H, Me), 1.18-1.41 (m, 2H, CH_2CH_3), 1.57-1.68 (m, 4H, $\text{COCH}_2 + \text{NH}$), 3.90 (t, $J=6.8$ Hz, 1H, CHNH_2), 6.90-7.15 (m, 3H, Ar), 7.22-7.33 (m, 1H, Ar).
	δ 0.89 (t, 3H, Me), 1.14-1.40 (m, 2H, CH_2CH_3), 1.55-1.70 (m, 4H, COCH_2), 3.88 (t, $J=6.8$ Hz, 1H, CHNH_2), 6.90-7.10 (m, 2H, Ar), 7.23-7.30 (m, 2H, Ar).
	δ 0.89 (t, $J=7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.18-1.38 (m, 2H, CH_2CH_3), 1.48-1.67 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 3.87 (t, $J=6.8$ Hz, 1H, CHNH_2), 7.21-7.31 (m, 4H, Ar)
	δ 0.90 (t, $J=7.2$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.21-1.40 (m, 2H, CH_2CH_3), 1.48 (brs, 2H, NH_2), 1.57-1.69 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.33 (s, 3H, Ar-Me), 3.85 (t, $J=7.0$ Hz, 1H, CHNH_2), 7.11-7.26 (m, 4H, Ar)
	δ 0.90 (t, $J=7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.17-1.35 (m, 2H, CH_2CH_3), 1.43 (brs, 2H, NH_2), 1.56-1.68 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.80 (s, 3H, OMe), 3.84 (t, $J=6.8$ Hz, 1H, CHNH_2), 6.86 (d, $J=8.6$ Hz, 2H, Ar) 7.24 (d, $J=8.6$ Hz, 2H, Ar)

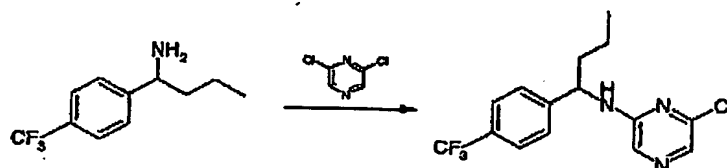
26.

Example 7**3-Amino-3-phenylpropan-1-ol**

To a suspension of 3-amino-3-phenylpropanoic acid (2.0 g, 12.1 mmol) in dry THF (45 mL) cooled to 0 °C under N₂ was added portionwise over 20 minutes solid LiAlH₄ (920 mg, 24.2 mmol). Stirring was continued at room temperature for 24 h. after which time solid Na₂SO₄·10H₂O was added with stirring until only a heavy white precipitate was present. The organic layer was diluted with ether and filtered through Celite® and the concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and extracted with 1N HCl (3 x 40 mL). The aqueous layers were combined and basified to pH~12 with 5M NaOH. The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases dried (Na₂SO₄) and concentrated *in vacuo* to separate the product which was used without further purification (0.9g, 49%).

¹H-n.m.r. (CDCl₃) δ 1.84-1.94 (m, 2H, CH₂CH₂OH), 2.68 (br s, 1H, NH₂), 3.79 (t, *J* = 5.8Hz, 2H, CH₂CH₂OH), 4.08-4.15 (m, 1H, CHNH₂), 4.77 (q, 1H, CH), 7.21-7.38 (m, 5H, Ar-H)

27.

Example 8**6-Chloro-N-[1-(4-(trifluoromethyl)phenyl)butyl]pyrazin-2-amine**

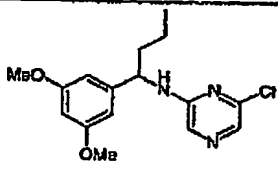
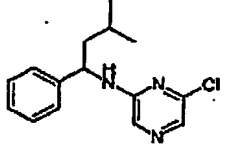
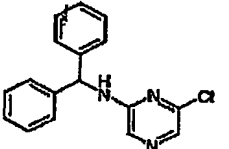
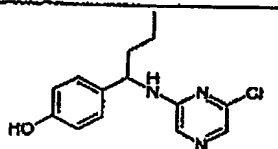
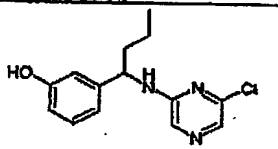
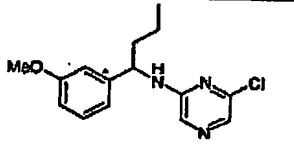
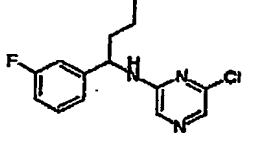
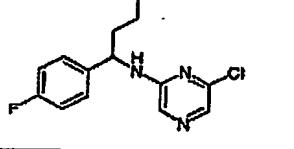
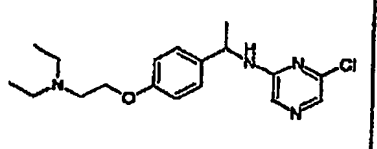
To a solution of 1-[4-(trifluoromethyl)phenyl]butan-1-amine (0.40 g, 1.9 mmol) and 2,6-dichloropyrazine (0.55 g, 3.7 mmol) in 1,4-dioxane (6 mL) was added anhydrous potassium carbonate (0.39 g, 2.8 mmol). The resulting mixture was heated at reflux for 18 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and H₂O. The organic phase was collected, dried and concentrated. The residue was purified by flash chromatography eluting with ethyl acetate-hexane (1:1) to give pure product (0.03 g, 5%).

¹H-n.m.r. (CDCl₃) δ 0.95 (t, *J*=7.4Hz, 3H CH₃), 1.39 (m, 2H, CH₂), 1.81 (m, 2H, CH₂), 4.77 (q, 1H, CH), 5.09 (br d, 1H, NH), 7.42–7.62 (m, 5H, Ar-H), 7.80 (s, 1H, pyraz-H)

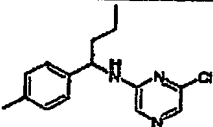
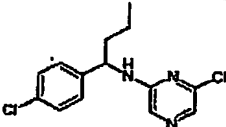
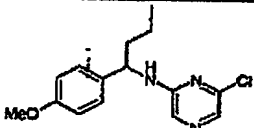
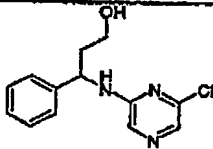
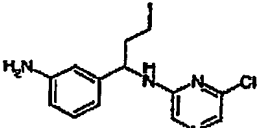
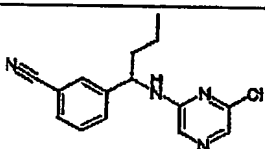
Using similar procedures the following compounds were prepared.

Compound	¹ H-n.m.r. (CDCl ₃)
	δ 0.95 (t, <i>J</i> =7.4Hz, 3H, CH ₃), 1.39 (m, 2H, CH ₂), 1.82 (m, 2H, CH ₂), 4.78 (q, 1H, CH), 5.12 (br d, 1H, NH), 7.41–7.81 (m, 6H, Ar-H).
	δ 0.94 (t, <i>J</i> =7.4Hz, 3H CH ₃), 1.38 (m, 2H, CH ₂), 1.83 (m, 2H, CH ₂), 2.34 (s, 3H, CH ₃ -Ar), 4.59 (m, 2H, CH × 2), 5.10 (d, 1H, NH), 7.09–7.22 (m, 4H, Ar-H), 7.59 (s, 1H, pyraz-H), 7.77 (s, 1H, pyraz-H).
	δ 0.94 (t, <i>J</i> =7.4Hz, 3H CH ₃), 1.37 (m, 2H, CH ₂), 1.81 (m, 2H, CH ₂), 2.46 (s, 3H, CH ₃ -S), 4.51 (q, 1H, CH), 4.63 (q, 1H, CH), 5.09 (d, 1H, NH), 7.23 (s, 4H, Ar-H), 7.58 (s, 1H, pyraz-H), 7.77 (s, 1H, pyraz-H).
	δ 0.95 (t, <i>J</i> =7.4Hz, 3H, CH ₃), 1.37 (m, 2H, CH ₂), 1.95 (m, 2H, CH ₂), 5.45 (m, 2H, CH + NH), 6.90–7.18 (m, 3H, Ar-H), 7.76 (s, 2H, Ar-H)

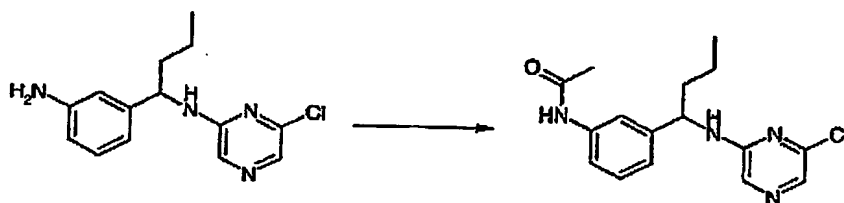
28.

	δ 0.93 (t, $J=7.4$ Hz, 3H CH_3), 1.38 (m, 2H, CH_2), 1.78 (m, 2H, CH_2), 3.76 (s, 6H, $\text{CH}_3\text{-O}$), 4.57 (q, $J=6$ Hz, 1H, CH), 5.15 (d, 1H, NH), 6.35 (m, 1H, Ar-H), 6.46 (m, 2H, Ar-H), 7.60 (s, 1H, pyraz-H), 7.77 (s, 1H, pyraz-H).
	δ 0.96 (t, $J=6.6$ Hz, 6H, 2xMe), 1.58-1.80 (m, 3H, $\text{CH}_2\text{CH}_2\text{Me}$), 4.67-4.77 (m, 1H, CHNH), 5.10 (br d, $J=6.8$ Hz, 1H, NH), 7.21-7.33 (m, 5H, Ar) 7.60 (s, 1H, pyraz-H), 7.77 (s, 1H, pyraz-H)
	δ 5.38 (br s, 1H, CHNH), 5.95 (br d, $J=6.2$ Hz, 1H, NH), 7.21-7.39 (m, 10H, 2xPh) 7.68 (s, 1H, pyraz-H), 7.83 (s, 1H, pyraz-H)
	δ 0.93 (t, $J=7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.17-1.44 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.63-1.73 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.51-4.62 (m, 1H, CHNH), 5.10 (br d, $J=6.4$ Hz, 1H, NH), 6.76 (d, $J=8.8$ Hz, 2H, Ar), 7.00 (d, $J=8.8$ Hz, 1H, Ar), 7.16 (d, $J=8.8$ Hz, 2H, Ar), 7.58 (s, 1H, pyraz-H), 7.77 (s, 1H, pyraz-H)
	δ 0.93 (t, $J=7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.26-1.44 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.73-1.85 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.52-4.63 (m, 1H, CHNH), 5.22 (br d, $J=6.8$ Hz, 1H, NH), 6.69-6.87 (m, 3H, Ar), 7.14-7.22 (m, 1H, Ar), 7.57 (s, 1H, pyraz-H), 7.76 (s, 1H, pyraz-H)
	δ 0.94 (t, $J=7.4$ Hz, 3H, Me), 1.30-1.49 (m, 2H, CH_2), 1.75-1.88 (m, 2H, CH_2), 3.79 (s, 3H, OMe), 4.62 (q, $J=7.2$ Hz, 1H, $\text{CHCH}_2\text{CH}_2\text{CH}_3$), 5.13 (br d, $J=6.8$ Hz, 1H, NH), 6.78-6.92 (m, 3H, Ar), 7.21-7.29 (m, 1H, Ar), 7.60 (s, 3H, pyraz-H), 7.77 (s, 1H, pyraz-H)
	δ 0.94 (t, $J=7.4$ Hz, 3H, Me), 1.27-1.46 (m, 2H, CH_2), 1.75-1.86 (m, 2H, CH_2), 4.69 (q, $J=7.0$ Hz, 1H, $\text{CHCH}_2\text{CH}_2\text{CH}_3$), 5.16 (br d, $J=6.8$ Hz, 1H, NH), 6.90-7.12 (m, 3H, Ar), 7.24-7.35 (m, 1H, Ar), 7.61 (s, 1H, pyraz-H), 7.79 (s, 1H, pyraz-H)
	δ 0.93 (t, $J=7.4$ Hz, 3H, Me), 1.25-1.47 (m, 2H, CH_2), 1.70-1.87 (m, 2H, CH_2), 4.66 (q, $J=7.1$ Hz, 1H, $\text{CHCH}_2\text{CH}_2\text{CH}_3$), 5.13 (br d, $J=6.6$ Hz, 1H, NH), 6.97-7.05 (m, 2H, Ar), 7.59-7.78 (m, 2H, Ar), 7.59 (s, 1H, pyraz-H), 7.78 (s, 1H, pyraz-H)
	δ 1.07 (t, $J=7.4$ Hz, 6H, 2x CH_2CH_3), 1.55 (d, $J=6.8$ Hz, 3H, CHCH_3), 2.64 (q, 4H, 2x CH_2CH_3), 2.87 (t, $J=6.4$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{N}$), 4.03 (t, $J=6.4$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{N}$), 4.80-4.85 (m, 1H, CHMe), 5.03 (br d, $J=6.8$ Hz, 1H, NH), 6.87 (d, $J=8.6$ Hz, 2H, Ar), 7.25 (d, $J=8.6$ Hz, 2H, Ar), 7.60 (s, 3H, pyraz-H), 7.78 (s, 1H, pyraz-H)

29.

	δ 0.93 (t, $J=7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.26-1.44 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.74-1.88 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.32 (s, 3H, Ar-Me), 4.57-4.67 (m, 1H, CHNH), 5.10 (br d, $J=6.2$ Hz, NH), 7.11-7.20 (m, 4H, Ar), 7.58 (s, 1H, pyraz-H), 7.76 (s, 1H, pyraz-H)
	δ 0.94 (t, $J=7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.26-1.45 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.74-1.87 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.61-4.71 (m, 1H, CHNH), 5.06 (br d, $J=6.4$ Hz, NH), 7.23-7.33 (m, 4H, Ar), 7.58 (s, 1H, pyraz-H), 7.79 (s, 1H, pyraz-H)
	δ 0.93 (t, $J=7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.26-1.43 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.74-1.88 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.78 (s, 3H, OMe), 4.55 (m, 1H, CHNH), 5.08 (br d, $J=6.8$ Hz, 1H, NH), 6.86 (d, $J=8.6$ Hz, 2H, Ar), 7.23 (d, $J=8.6$ Hz, 2H, Ar), 7.58 (s, 1H, pyraz-H), 7.76 (s, 1H, pyraz-H)
	δ 2.04-2.15 (m, 2H, $\text{CH}_2\text{CH}_2\text{OH}$), 3.74 (t, $J=4.8$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{OH}$), 4.98-5.08 (m, 1H, CHNH), 5.69 (br d, $J=7.0$ Hz, 1H, NH), 7.39 (m, 5H, Ar), 7.66 (s, 1H, pyraz-H), 7.77 (s, 1H, pyraz-H)
	δ 0.94 (t, $J=7.2$ Hz, 3H, Me), 1.27-1.46 (m, 2H, CH_2), 1.74-1.86 (m, 2H, CH_2), 3.66 (br s, 2H, NH_2), 4.48-4.59 (m, 1H, $\text{CHCH}_2\text{CH}_2\text{CH}_3$), 5.06 (br d, $J=7.0$ Hz, 1H, NH), 6.54-6.71 (m, 3H, Ar), 7.11 (t, $J=7.8$ Hz, 1H, Ar), 7.60 (s, 1H, pyraz-H), 7.77 (s, 1H, pyraz-H)
	δ 0.96 (t, $J=7.3$ Hz, 3H, Me), 1.26-1.51 (m, 2H, CH_2), 1.77-1.90 (m, 2H, CH_2), 4.77 (q, $J=6.8$ Hz, 1H, $\text{CHCH}_2\text{CH}_2\text{CH}_3$), 5.07 (d, $J=7.4$ Hz, 1H, NH), 7.41-7.63 (m, 4H, Ar), 7.64 (s, 1H, pyraz-H), 7.81 (s, 1H, pyraz-H)

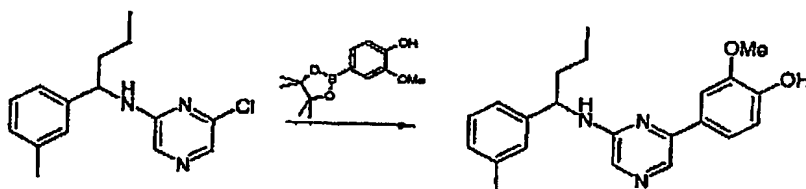
30.

Example 9*N*-(3-[1-[(6-Chloropyrazin-2-yl)amino]butyl]phenyl)acetamide

To a stirred solution of *N*[1-(3-aminophenyl)butyl]-6-chloropyrazin-2-amine (0.10 g, 0.36 mmol) and triethylamine (100 μ L, 0.72 mmol) in dichloromethane (3 mL) cooled to 0 °C was added acetyl chloride (31 μ L, 0.43 mmol). The resulting mixture was stirred at room temperature for 18 h. then diluted with dichloromethane (10 mL) and washed with H₂O (10 mL) and brine (10 mL). The organic phase was collected, dried and concentrated and the residue purified by flash chromatography eluting with ethyl acetate-hexane (1:1) to give pure product (94 mg, 82%).

¹H-n.m.r. (CDCl₃) δ 0.93 (t, J =7.4Hz, 3H, Me), 1.28-1.43 (m, 2H, CH₂), 1.76-1.85 (m, 2H, CH₂), 2.16 (s, 3H, COCH₃), 4.48-4.59 (m, 1H, CHCH₂CH₂CH₃), 5.15 (br d, J =6.8Hz, 1H, NH), 7.06 (d, J =7.4Hz, 1H, Ar), 7.23-7.33 (m, 3H, Ar), 7.54 (s, 1H, CONH), 7.60 (s, 1H, pyraz-H), 7.77 (s, 1H, pyraz-H).

31.

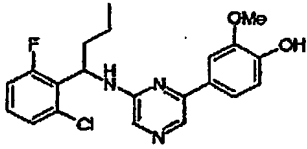
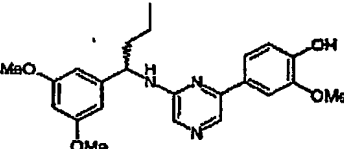
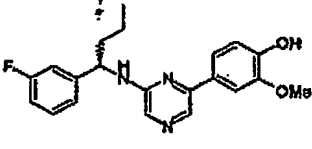
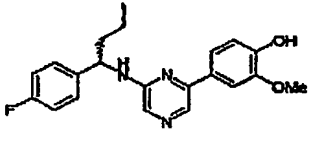
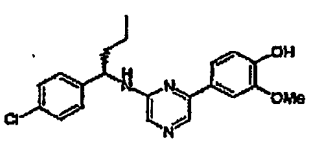
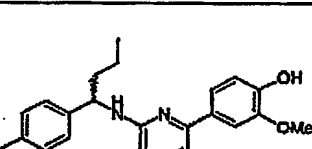
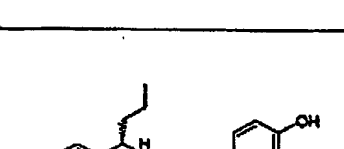
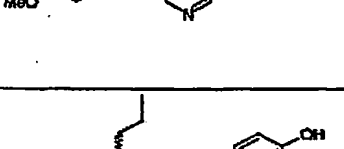
Example 10**6-Chloro-N-[1-(4-methylphenyl)butyl]pyrazin-2-amine**

Under a nitrogen atmosphere a mixture of 6-chloro-N-[1-(3-methylphenyl)butyl]pyrazin-2-amine (0.21 g, 0.76 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.23 g, 91 mmol), tetrakis(triphenylphosphine)palladium(0) (90 mg, 0.08 mmol) in toluene-*n*-propanol (4 mL, 3:1) was treated with 2M aqueous sodium carbonate solution (0.4 mL, 0.84 mmol). The resulting mixture was stirred vigorously whilst being heated under reflux for 22 hours. Once cool ethyl acetate was added and the mixture dried (MgSO_4) and filtered. Removal of solvent *in vacuo* then yielded crude product, which was purified by column chromatography using dichloromethane:diethyl ether (90:10) as eluent to furnish (0.165 g, 60%).

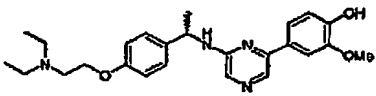
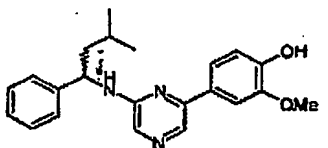
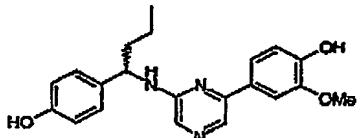
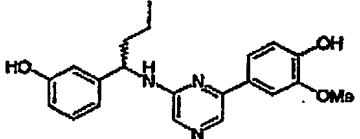
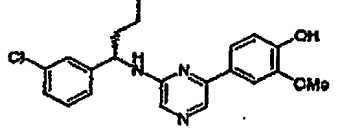
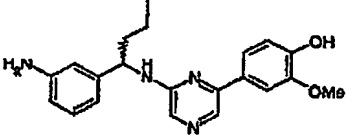
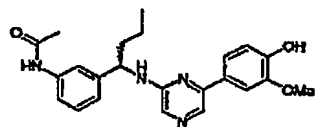
$^1\text{H-n.m.r.}$ (CDCl_3) δ 0.95 (t, 3H, CH_3), 1.42 (m, 2H, CH_2), 1.82 (m, 2H, CH_2), 2.33 (s, 3H, CH_3 -Ar), 3.94 (s, 3H, CH_3 -O), 4.75 (m, 1H, CH), 5.09 (d, 1H, NH), 6.25 (br s, 1H, OH), 6.94-7.50 (m, 7H, Ar-H), 7.66 (s, 1H, pyraz.-H), 8.20 (s, 1H, pyraz.-H).

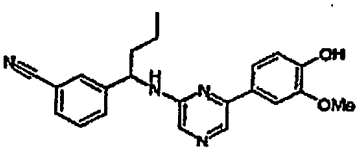
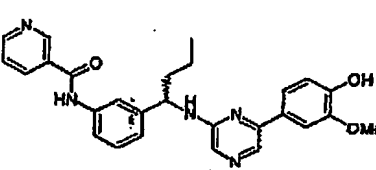
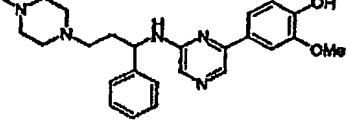
Using similar procedures the following compounds were prepared.

Compound	$^1\text{H-n.m.r.}$ (CDCl_3)	m/z (ES)
	δ 0.95 (t, 3H, CH_3), 1.42 (m, 2H, CH_2), 1.85 (m, 2H, CH_2), 2.45 (s, 3H, CH_3 -S), 3.94 (s, 3H, CH_3 -O), 4.75 (q, 1H, CH), 5.01 (d, 1H, NH), 5.96 (br s, 1H, OH), 6.94-7.44 (m, 7H, Ar-H), 7.65 (s, 1H, py-H), 8.20 (s, 1H, py-H).	
	δ 0.95 (t, 3H, CH_3), 1.43 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 3.76 (s, 6H, 2 x CH_3 -O), 3.94 (s, 3H, CH_3 -O), 4.70 (q, 1H, CH), 5.03 (d, 1H, NH), 6.07 (br s, 1H, OH).	
	δ 0.98 (t, 3H, CH_3), 1.43 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 3.92 (s, 3H, CH_3 -O), 4.94 (m, 2H, CH + NH), 6.96 (d, 1H, Ar-H), 7.36-7.64 (m, 6H, Ar-H), 7.69 (s, 1H, pyraz.-H), 8.22 (s, 1H, pyraz.-H).	

	δ 0.95 (t, 3H, CH ₃), 1.42 (m, 2H, CH ₂), 1.82 (m, 2H, CH ₂), 2.33 (s, 3H, CH ₃ -Ar), 3.94 (s, 3H, CH ₃ -O), 4.74 (q, 1H, CH), 5.29 (d, 1H, NH), 6.25 (br s, 1H, OH), 6.94-7.50 (m, 7H, Ar-H), 7.66 (s, 1H, pyraz-H), 8.20 (s, 1H, pyraz-H).	
	δ 0.93 (t, $J=7.4$ Hz, 3H CH ₃), 1.38 (m, 2H, CH ₂), 1.78 (m, 2H, CH ₂), 3.76 (s, 6H, CH ₃ -O), 4.57 (q, $J=6$ Hz, 1H, CH), 5.15 (d, 1H, NH), 6.35 (m, 1H, Ar-H), 6.46 (m, 2H, Ar-H), 7.60 (s, 1H, pyraz-H), 7.77 (s, 1H, pyraz-H).	
	δ 0.96 (t, $J=7.4$ Hz, 3H, CH ₂ CH ₂ CH ₃), 1.35-1.51 (m, 2H, CH ₂ CH ₂ CH ₃), 1.78-1.92 (m, 2H, CH ₂ CH ₂ CH ₃), 3.94 (s, 3H, OMe), 4.76-4.86 (m, 1H, CHNH), 5.01 (br d, $J=6.0$ Hz, 1H, NH), 5.91 (br s, 1H, OH), 6.96 (d, $J=8.0$ Hz, 1H, Ar), 7.06-7.42 (m, 6H, Ar) 7.72 (br s, 1H, pyraz-H), 8.22 (br s, 1H, pyraz-H)	368 (M+H) ⁺
	δ 0.96 (t, $J=7.1$ Hz, 3H, CH ₂ CH ₂ CH ₃), 1.30-1.48 (m, 2H, CH ₂ CH ₂ CH ₃), 1.73-1.93 (m, 2H, CH ₂ CH ₂ CH ₃), 3.94 (s, 3H, OMe), 4.73-4.83 (m, 1H, CHNH), 5.02 (br d, $J=6.4$ Hz, 1H, NH), 6.02 (br s, 1H, OH), 6.94-7.05 (m, 3H, Ar), 7.30-7.44 (m, 4H, Ar), 7.66 (s, 1H, pyraz-H), 8.21 (s, 1H, pyraz-H)	368 (M+H) ⁺
	δ 0.95 (t, $J=7.4$ Hz, 3H, CH ₂ CH ₂ CH ₃), 1.30-1.48 (m, 2H, CH ₂ CH ₂ CH ₃), 1.72-1.95 (m, 2H, CH ₂ CH ₂ CH ₃), 3.91 (s, 3H, OMe), 4.72-4.82 (m, 1H, CHNH), 5.07 (br d, $J=6.2$ Hz, 1H, NH), 6.25 (br s, 1H, OH), 6.95 (d, $J=8.6$ Hz, 1H, Ar), 7.29 (br s, 4H, Ar), 7.39-7.42 (m, 2H, Ar), 7.76 (s, 1H, pyraz-H), 8.21 (s, 1H, pyraz-H)	384 (M+H) ⁺
	δ 0.95 (t, $J=7.4$ Hz, 3H, CH ₂ CH ₂ CH ₃), 1.30-1.52 (m, 2H, CH ₂ CH ₂ CH ₃), 1.75-1.94 (m, 2H, CH ₂ CH ₂ CH ₃), 2.32 (s, 3H, Ar-Me), 3.95 (s, 3H, OMe), 4.70-4.80 (m, 1H, CHNH), 5.03 (br d, $J=6.6$ Hz, 1H, NH), 6.04 (br s, 1H, OH), 6.96 (d, $J=8.2$ Hz, 1H, Ar), 7.13 (d, $J=8.1$ Hz, 1H, Ar), 7.26 (d, $J=8.1$ Hz, 1H, Ar), 7.65 (s, 1H, pyraz-H), 8.19 (s, 1H, pyraz-H)	364 (M+H) ⁺
	δ 0.95 (t, $J=7.4$ Hz, 3H, CH ₂ CH ₂ CH ₃), 1.29-1.51 (m, 2H, CH ₂ CH ₂ CH ₃), 1.73-1.93 (m, 2H, CH ₂ CH ₂ CH ₃), 3.77 (s, 3H, OMe), 3.95 (s, 3H, OMe), 4.68-4.78 (m, 1H, CHNH), 5.03 (br d, $J=6.2$ Hz, 1H, NH), 6.10 (br s, 1H, OH), 6.85 (d, $J=8.4$ Hz, 2H, Ar), 6.96 (d, $J=8.4$ Hz, 1H, Ar), 7.28 (d, $J=8.4$ Hz, 2H, Ar), 7.40-7.49 (m, 2H, Ar), 7.65 (s, 1H, pyraz-H), 8.20 (s, 1H, pyraz-H)	380 (M+H) ⁺
	δ 0.96 (t, $J=7.2$ Hz, 3H, CH ₂ CH ₂ CH ₃), 1.39-1.50 (m, 2H, CH ₂ CH ₂ CH ₃), 1.79 (m, 2H, CH ₂ CH ₂ CH ₃), 3.78 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.71-4.81 (m, 1H, CHNH), 5.02 (br d, $J=6.0$ Hz, NH), 5.98 (s, 1H, OH), 6.74-6.80 (m, 1H, Ar), 6.96 (d, $J=8.4$ Hz, 1H,	380 (M+H) ⁺

33.

	Ar), 7.20-7.28 (m, 1H, Ar), 7.41-7.48 (m, 2H, Ar), 7.67 (s, 1H, pyraz-H), 8.20 (s, 1H, pyraz-H)	
	δ 1.07 (t, $J=7.2$ Hz, 6H, $2 \times \text{CH}_2\text{CH}_3$), 1.58 (d, $J=6.4$ Hz, 3H, CHCH_3), 2.64 (q, $J=7.2$ Hz, 4H, $2 \times \text{CH}_2\text{CH}_3$), 2.87 (t, $J=6.4$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{N}$), 3.94 (s, 3H, OMe), 4.03 (t, $J=6.4$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{N}$), 4.88-4.97 (m, 2H, $\text{CHMe} + \text{NH}$), 6.84-6.98 (m, 3H, Ar), 7.26-7.49 (m, 4H, Ar), 7.65 (s, 1H, pyraz-H), 8.21 (s, 1H, pyraz-H)	437 (M+H) ⁺
	δ 0.96 (d, $J=9.5$ Hz, 3H, $\text{CH}_2(\text{CH}_3)\text{CH}_3$), 0.99 (d, $J=9.9$ Hz, 3H, $\text{CH}(\text{CH}_3)\text{CH}_3$), 1.63-1.86 (m, 3H, $\text{CH}(\text{CH}_3)\text{CH}_3$ and CH_2), 3.94 (s, 3H, OMe), 4.83-4.94 (m, 1H, CHNH), 5.01 (brd, $J=7.0$ Hz, 1H, NH), 6.05 (brs, 1H, OH), 6.96 (d, $J=8.4$ Hz, 1H, Ar), 7.22-7.48 (m, 7H, Ar), 7.67 (s, 1H, pyraz-H), 8.19 (s, 1H, pyraz-H)	364 (M+H) ⁺
	δ 0.94 (t, $J=7.2$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.32-1.47 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.76-1.90 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.94 (s, 3H, OMe), 4.57-4.68 (m, 1H, CHNH), 5.11 (br d, $J=6.2$ Hz, 1H, NH), 6.70 (d, $J=8.5$ Hz, 2H, Ar), 6.96 (d, $J=7.6$ Hz, 1H, Ar), 7.16 (d, $J=8.5$ Hz, 2H, Ar), 7.41-7.49 (m, 2H, Ar), 7.62 (s, 1H, pyraz-H), 8.19 (s, 1H, pyraz-H)	366 (M+H) ⁺
	δ 0.94 (t, $J=7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.33-1.49 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.76-1.90 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.94 (s, 3H, OMe), 4.65-4.75 (m, 1H, CHNH), 5.04 (br d, $J=6.2$ Hz, 1H, NH), 6.68-6.73 (m, 1H, Ar), 6.82-6.98 (m, 3H, Ar), 7.17 (t, $J=7.8$ Hz, 1H, Ar), 7.45-7.47 (m, 2H, Ar), 7.62 (s, 1H, pyraz-H), 8.18 (s, 1H, pyraz-H)	366 (M+H) ⁺
	δ 0.96 (t, $J=7.2$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.39-1.50 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.77-1.92 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.94 (s, 3H, OMe), 4.74-4.84 (m, 1H, CHNH), 4.99 (br d, $J=6.0$ Hz, 1H, NH), 5.87 (br s, 1H, OH), 6.96 (d, $J=8.8$ Hz, 1H, Ar), 7.69 (br s, 1H, pyr), 8.24 (br s, 1H, pyr)	384 (M+H) ⁺
	δ 0.95 (t, $J=7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.35-1.50 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.77-1.88 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.64 (br s, 2H, NH_2), 3.96 (s, 3H, OMe), 4.67 (q, $J=6.8$ Hz, 1H, CH), 4.99 (br d, $J=6.8$ Hz, 1H, NH), 5.95 (br s, 1H, OH), 6.53-6.58 (m, 1H, Ar), 6.68 (m, 1H, Ar), 6.75-6.78 (m, 1H, Ar), 6.97 (d, $J=8.4$ Hz, 1H, Ar), 7.10 (t, $J=7.8$ Hz, 1H, Ar), 7.41-7.55 (m, 2H, Ar), 7.66 (s, 1H, pyraz-H), 8.20 (s, 1H, pyraz-H)	365 (M+H) ⁺
	δ 0.96 (t, $J=7.2$ Hz, 3H, Me), 1.35-1.52 (m, 2H, CH_2), 1.80-1.92 (m, 2H, CH_2), 2.14 (s, 3H, COCH_3), 3.95 (s, 3H, OMe), 4.78 (q, $J=6.8$ Hz, 1H, CH), 5.02 (br d, $J=6.2$ Hz, 1H, NH), 5.80 (s, 1H, OH), 6.96 (d, $J=7.8$ Hz, 1H, Ar), 7.11-7.22 (m, 2H, Ar), 7.30-7.47 (m, 4H, Ar), 7.57 (s, 1H, CONH), 7.67 (s, 1H, pyraz-H), 8.20 (s, 1H, pyraz-H)	

	<p>δ 0.97 (t, $J=7.4$Hz, 3H, Me), 1.33-1.52 (m, 2H, CH₂), 1.76-1.89 (m, 2H, CH₂), 3.94 (s, 3H, OCH₃), 4.88 (q, $J=6.8$Hz, 1H, CHCH₂CH₂CH₃), 5.07 (d, $J=7.4$Hz, 1H, NH), 6.96 (d, $J=7.8$Hz, 1H, Ar), 7.35-7.46 (m, 3H, Ar), 7.51-7.56 (m, 1H, Ar), 7.60-7.65 (m, 1H, Ar), 7.68-7.71 (m, 2H, Ar + pyraz-H), 8.23 (s, 1H, pyraz-H)</p>	
	<p>δ 0.93 (t, $J=7.4$Hz, 3H, Me), 1.32-1.52 (m, 2H, CH₂), 1.78-1.92 (m, 2H, CH₂), 3.88 (s, 3H, OMe), 4.79 (q, $J=6.8$Hz, 1H, CH), 5.25 (br d, $J=6.2$Hz, 1H, NH), 6.45 (br s, 1H, OH), 6.91 (d, $J=8.4$Hz, 1H, Ar), 7.15-7.53 (m, 6H, Ar), 7.63 (s, 1H, pyraz-H), 7.71 (br s, 1H, CONH), 8.10-8.17 (m, 1H, pyr-H), 8.14 (s, 1H, pyraz-H), 8.51 (m, 1H, pyr-H), 8.67 (dd, 1H, $J=4.8, 2.0$Hz, 1H, pyr-H), 9.06 (d, 1H, $J=2.0$Hz, 1H, pyr-H).</p>	
	<p>δ 1.84-2.17 (m, 2H, CH₂), 2.34 (s, 3H, NMe), 2.50-2.56 (m, 10H, CH₂N), 3.85 (s, 3H, OMe), 4.96-5.03 (m, 1H, CHNH), 6.90 (d, $J=7.8$Hz, 1H, Ar), 7.20-7.47 (m, 7H, Ar), 7.71 (s, 1H, pyraz-H), 8.15 (s, 1H, pyraz-H)</p>	

SCREENING

Compound Dilution

For screening purposes, compounds were diluted in 96 well plates at a concentration of 20 μ M. Plates were warmed at 37°C for 30 minutes before assay.

Establishment of TEL:JAK cell lines

The coding region encompassing nucleotides 1-487 of TEL was amplified by PCR using the oligonucleotides 5TEL (5' -GGA GGA TCC TGA TCT CTC TCG CTG TGA GAC-3') and 3TEL (5'-AGGC GTC GAC TTC TTC TTC ATG GTT CTG-3') and U937 mRNA as template. A BamHI site was present into the 5TEL Primer, a Sal I site was incorporated into the 3TEL primer. The regions encompassing the kinase domains of JAK2 (nucleotides 2994-3914; JAK2F 5'-ACGC GTC GAC GGT GCC TTT GAA GAC CGG GAT-3' ; JAK2R 5'-ATA GTT TAG CGG CCG CTC AGA ATG AAG GTC ATT T-3') and JAK3 (nucleotides 2520-3469; JAK3F 5'-GAA GTC GAC TAT GCC TGC CAA GAC CCC ACG ATC TT-3' ; JAK3R 5'-GGA TCT AGA CTA TGA AAA GGA CAG GGA GTG GTG TTT -3') were generated by PCR using Taq DNA Polymerase (Gibco/BRL) and U937 mRNA as template. A SalI site was incorporated into the forward primer of JAK2 and JAK3, a Not I site was incorporated into the JAK2 reverse primer and a Xba I site was added to the reverse primer of JAK3.

A TEL/Jak2 fusion was generated by digestion of the TELPCR product with BamHI /Sal I, digestion of the JAK2 PCR product with Sal I/ Not I followed by ligation and subcloning into the mammalian expression Vector pTRE 2 (Clontech) digested with BamHI-Not I (pTELJAK2). For JAK3 Sal I/ Not I cleaved kinase domain PCR product was ligated with BamHI /Sal I cleaved TELproduct followed by ligation into BamHI/Not I cleaved pTRE2 (pTELJAK3).

The growth factor dependent myelomonocytic cell line BaF3 bearing the pTET-off plasmid (Clontech) was transfected with either pTELJAK2 or pTELJAK3 and the cells selected for factor independent growth. BaF 3 wild type cells were cultured in DMEM 10% FCS, 10% WEHI 3B conditioned medium. BaF3 TEL/JAK cells were cultured in DMEM 10% Tet-System Approved FBS (without WEHI 3B conditioned medium).

Growth and Maintenance of Cancer Cell lines

K562 (Chronic Myeloid Leukemia), PC3 (Prostate Cancer), DU145 (Prostate Cancer), and Jurkat (T-cell Lymphoma) were obtained from the American Type Culture Collection (ATCC). K562 and Jurkat were grown in RPMI, with 10% FBS with Glutamax added. DU145 cells were cultured in

DMED, with 10% FBS and Glutamx and MEM non-essential amino acids added. PC3 cells were grown in F12K medium, with 10% FBS and Glutamx and MEM non-essential amino acids added. All cells were grown at 37°C in 5% CO₂.

Cellular assays were performed as follows:

Cell suspensions were prepared by harvesting cells from culture. (Cells used in this test should be in later log phase growth and high viability.) Cells were diluted in correct growth medium to 1.1x final concentration (from 50000 cell/mL to 200,000 cell/mL, depending on cell line).

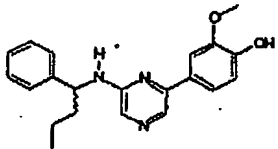
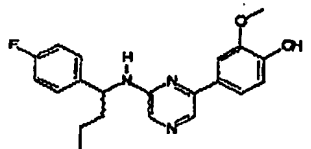
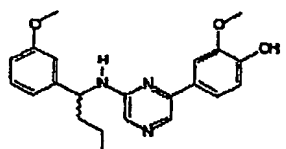
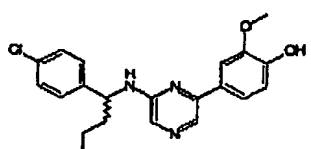
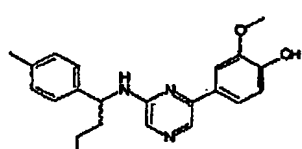
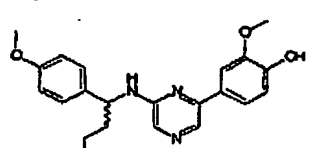
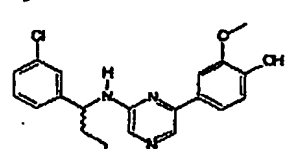
Compounds to be tested were added (10µL, 10X final concentration) to a flat bottom 96-well plate. The cellular suspension (90µL per well) was added, and the plate incubated for 40 hr at 37 °C, 5% CO₂. MTT (20 µL per well, 5mg/mL in PBS) was added and the plates were returned to the incubator for a further 6 hours. Lysis buffer (100 µL per well, 10% SDS, 0.01N HCl) was added and the plate stored in the incubator overnight. The plate was then read at 590 nm.

Results

The activity of a range of compounds is shown in Table 1. Compounds that exhibited a capacity to inhibit 50% of cellular growth at a concentration of 10µM or less are designated as "+"

37.

Table 1

CHEMISTRY	DU145	PC3	K562	Jurkat
 Chemistry 244	+	+	+	+
 Chemistry 277	+	-	-	+
 Chemistry 284	+	+	+	+
 Chemistry 286	+	-	+	+
 Chemistry 287	+	-	+	+
 Chemistry 288	+	+	+	+
 Chemistry 311	+	+	+	+

38.

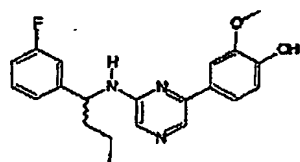
CHEMISTRY

DU145

PC9

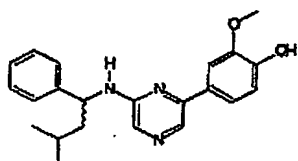
K562

Jurkat



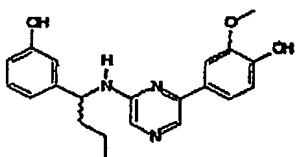
Chemistry 312

DU145	PC9	K562	Jurkat
+	+	+	+



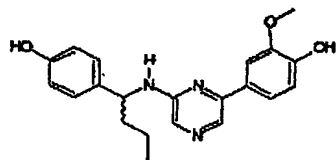
Chemistry 314

-	-	+	+
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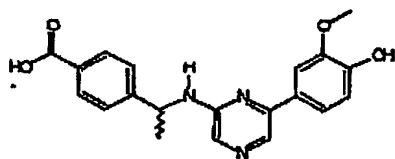
Chemistry 316

-	-	+	+
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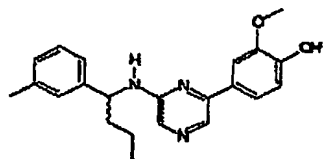
Chemistry 317

-	-	-	-
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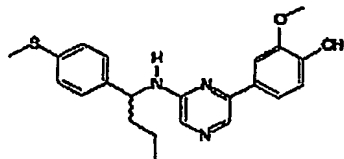
Chemistry 324

-	-	-	-
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Chemistry 326

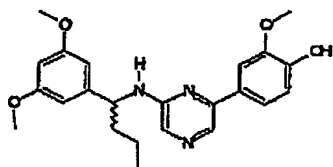
+	+	+	+
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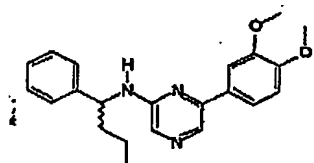
Chemistry 327

-	-	+	+
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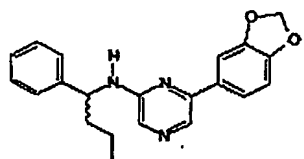
39.

CHEMISTRY

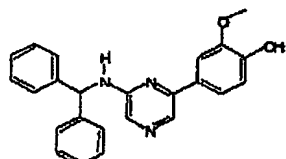
Chemistry 328



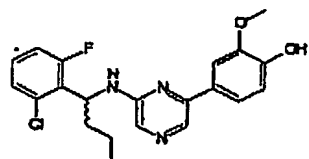
Chemistry 329



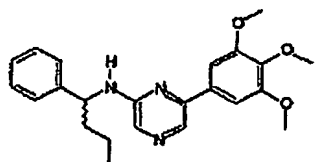
Chemistry 330



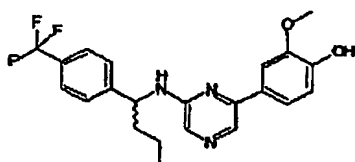
Chemistry 331



Chemistry 334



Chemistry 335



Chemistry 337

DU145	PC3	K562	Jurkat
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+	+	+	+
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+	+	+	+
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+	+	+	+
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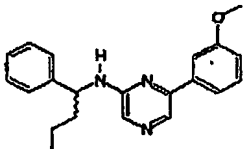
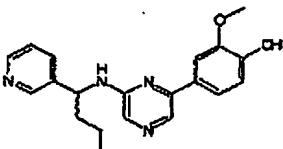
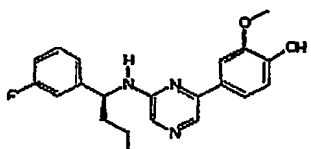
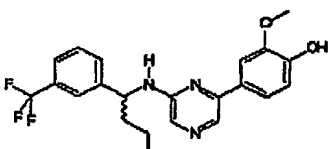
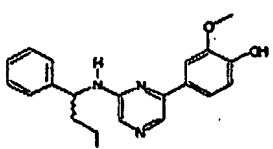
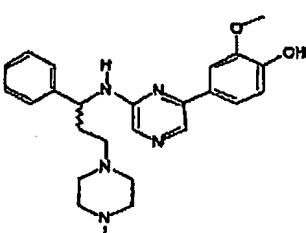
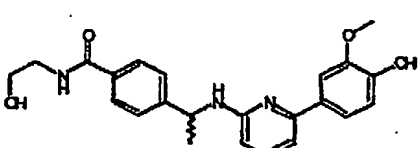
-	-	+	+
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+	-	+	+
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-	-	+	+
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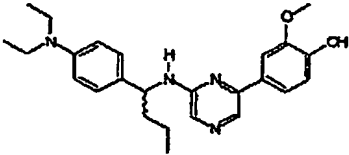
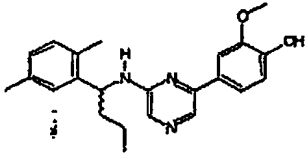
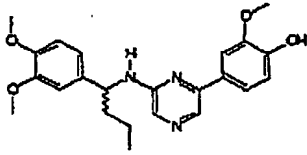
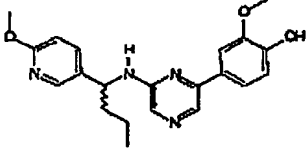
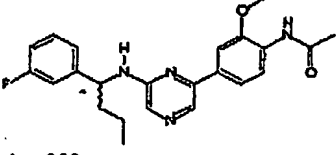
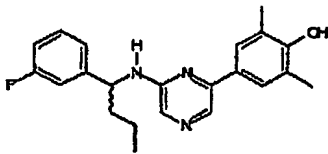
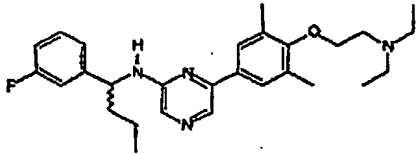
-	-	-	-
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40.

CHEMISTRY	DU145	PC3	K562	Jurkat
 Chemistry 345	-	-	+	+
 Chemistry 366	+	+	+	+
 Chemistry 367	+	+	+	+
 Chemistry 368	-	+	+	+
 Chemistry 371	-	-	-	+
 Chemistry 373	-	-	-	+
 Chemistry 374	-	-	-	-

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41.

CHEMISTRY	DU145	PC3	K562	Jurkat
	-	-	-	-
Chemistry 375				
	+	-	+	+
Chemistry 376				
	+	-	+	+
Chemistry 377				
	+	-	+	+
Chemistry 378				
	+	+	+	+
Chemistry 399				
	+	-	+	+
Chemistry 400				
	+	-	+	+
Chemistry 401				

42.

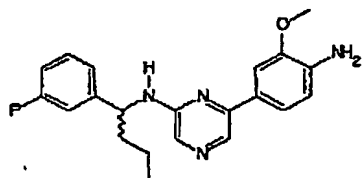
CHEMISTRY

DU145

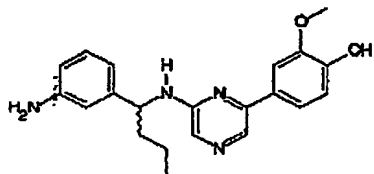
PC3

K562

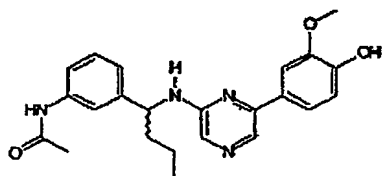
Jurkat



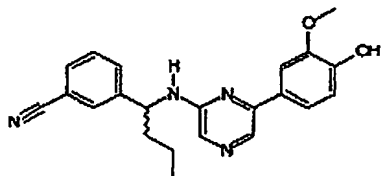
Chemistry 402



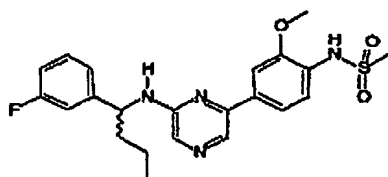
Chemistry 403



Chemistry 404



Chemistry 404



Chemistry 406

+ + + +

- + + +

- - - +

- - + +

- - + +

43.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Dated this 11th day of December, 2002

Cytopia Pty Ltd

Patent Attorneys for the Applicant:

**BLAKE DAWSON WALDRON PATENT
SERVICES**

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